Dysmenorrhoea

Search date July 2006

Michelle L Proctor and Cynthia M Farquhar

ABSTRACT

INTRODUCTION: Dysmenorrhoea may begin soon after the menarche, after which it often improves with age, or it may originate later in life after the onset of an underlying causative condition. Dysmenorrhoea is common, and in up to 20% of women it may be severe enough to interfere with daily activities. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for dysmenorrhoea? We searched: Medline, Embase, The Cochrane Library and other important databases up to July 2006 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 34 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: acupressure, acupuncture, aspirin, behavioural interventions, combined oral contraceptives, compound analgesics, fish oil, herbal remedies, magnesium, magnets, non-steroidal anti-inflammatory drugs, paracetamol, spinal manipulation, surgical interruption of pelvic nerve pathways, thiamine, toki-shakuyaku-san, topical heat, transcutaneous electrical nerve stimulation (TENS), vitamin B12, and vitamin E.

QUESTIONS

INTERVENTIONS

Key points

- Dysmenorrhoea may begin soon after the menarche, where it often improves with age, or may originate later in life after the onset of an underlying causative condition.

  Dysmenorrhoea is very common, and in up to 20% of women it may be severe enough to interfere with daily activities.

  Dysmenorrhoea is more likely in women who smoke, and those with an earlier age at menarche or longer duration of menstruation.

- NSAIDs, reduce moderate to severe pain in women with primary dysmenorrhoea compared with placebo, but we don't know whether any one NSAID is superior to the others.

  Aspirin, paracetamol, and compound analgesics may reduce pain in the short term, although few studies have been of good quality.

  The herbal remedy toki-shakuyaku-san may reduce pain after 6 months compared with placebo, but we don't know whether any other herbal remedy is beneficial.

  Thiamine and vitamin E may reduce pain compared with placebo in women with primary dysmenorrhoea.

- We don't know whether combined oral contraceptives reduce the pain of dysmenorrhoea, as studies have been small and have used products that are no longer available.

- Topical heat (about 39 °C) may be as effective as ibuprofen and more effective than paracetamol at reducing pain.

High frequency TENS may reduce pain compared with sham TENS, but seems to be less effective than ibuprofen.

Acupressure may be more effective than sham acupressure at relieving dysmenorrhoea, and may be as effective as ibuprofen at relieving pain.

Spinal manipulation seems to be no more effective than placebo at reducing pain after 1 month in women with primary dysmenorrhoea.

We don't know whether acupuncture, relaxation or aerobic exercise, fish oil, magnesium, vitamin B12, surgical interruption of pelvic nerve pathways, or magnets reduce dysmenorrhoea, as few studies have been found.

DEFINITION

Dysmenorrhoea is painful menstrual cramps of uterine origin. It is commonly divided into primary dysmenorrhoea (pain without organic pathology) and secondary dysmenorrhoea (pelvic pain associated with an identifiable pathological condition, such as endometriosis [see endometriosis] or ovarian cysts). The initial onset of primary dysmenorrhoea is usually shortly after menarche (6–12 months), when ovulatory cycles are established. Pain duration is commonly 8–72 hours and is usually associated with the onset of menstrual flow. Secondary dysmenorrhoea can also occur at any time after menarche, but may arise as a new symptom during a woman's fourth and fifth decades, after the onset of an underlying causative condition. [1] This review deals with both primary and secondary dysmenorrhoea; however, it should be noted that most RCTs are in women with primary dysmenorrhoea. Endometriosis, which can cause secondary dysmenorrhoea, is covered in a separate review (see endometriosis).

INCIDENCE/ PREVALENCE

Variations in the definition of dysmenorrhoea make it difficult to determine prevalence precisely. Studies tend to report on prevalence in adolescent girls, and the type of dysmenorrhoea is not always specified. Adolescent girls tend to have a higher prevalence of primary dysmenorrhoea than older women, as primary dysmenorrhoea can improve with age (see Prognosis). Secondary dysmenorrhoea rates may be lower in adolescents, as onset of causative conditions may not yet have occurred. Therefore, the results from prevalence studies of adolescents may not always be extrapolated to older women, or be accurate estimates of the prevalence of secondary dysmenorrhoea. However, various types of studies have found a consistently high prevalence in women of different ages and nationalities. One systematic review (search date 1996) of the prevalence of chronic pelvic pain, summarising both community and hospital surveys from developed countries, estimated prevalence to be 45–95%. [2] A second systematic review of studies in developing countries (search date 2002) found that 25–50% of adult women and about 75% of adolescents experienced pain with menstruation, with 5–20% reporting severe dysmenorrhoea or pain that prevents them from participating in their usual activities. [3] Additional studies of prevalence are summarised in Table 1 (see table 1, p 21). [4] [5] [6] [7] [8] [9] [10]

AETIOLOGY/ RISK FACTORS

A longitudinal study of a representative sample of women born in 1962, residing in Göteborg, Sweden, found that the severity of dysmenorrhoea was significantly associated with the duration of menstrual flow (average duration of menstrual flow was 5.0 days for women with no dysmenorrhoea and 5.8 days for women with severe dysmenorrhoea, where severe dysmenorrhoea was defined as pain that did not respond well to analgesics and clearly inhibited daily activity; $P < 0.001$; WMD –0.80, 95% CI –1.36 to –0.24); younger age at menarche (13.1 years in women without dysmenorrhoea *v* 12.6 years in women with severe dysmenorrhoea; $P < 0.01$; WMD 0.50, 95% CI 0.09 to 0.91); and cigarette smoking (41% of smokers and 26% of non-smokers experienced moderate or severe dysmenorrhoea). [11] There is also some evidence of a dose–response relationship between exposure to environmental tobacco smoke and increased incidence of dysmenorrhoea. [12]

PROGNOSIS

Primary dysmenorrhoea is a chronic recurring condition that affects most young women. Studies of the natural history of this condition are sparse. One longitudinal study in Scandinavia found that primary dysmenorrhoea often improves in the third decade of a woman's reproductive life, and is also reduced after childbirth. [11] We found no studies that reliably examined the relationship between the prognosis of secondary dysmenorrhoea and the severity of the underlying pathology, such as endometriosis.

AIMS OF INTERVENTION

To relieve pain from dysmenorrhoea, with minimal adverse effects.

OUTCOMES

Pain relief, measured either by a visual analogue scale, other pain scales (such as the TOTPAR [TOPAR] score, TOTPAR-8 [TOPAR-8], or SPID-8), or as a dichotomous outcome (pain relief achieved yes/no); overall improvement in dysmenorrhoea measured by change in dysmenorrhoeic symptoms either self reported or observed, quality of life scales, or other similar measures such as the Menstrual Distress or Menstrual Symptom Questionnaires; proportion of women requiring analgesics in addition to their assigned treatment; proportion of women reporting activity restriction

or absences from work or school and hours or days of absence as a more selective measure; adverse effects of treatment (incidence and type of adverse effects).

METHODS

BMJ Clinical Evidence search and appraisal July 2006. The following databases were used to identify studies for this review: Medline 1966 to July 2006, Embase 1980 to July 2006, and The Cochrane Library, Issue 2, 2006. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) ¯for all databases, Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). Abstracts of the studies retrieved were assessed independently by two information specialists using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless the interventions could not be "blinded". In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are continually added to the review as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 23).

QUESTION What are the effects of treatments for dysmenorrhoea?

OPTION NSAIDS (OTHER THAN ASPIRIN)

Pain

Compared with placebo NSAIDs may reduce pain after 8–12 hours compared with placebo in women with primary dysmenorrhoea (very low-quality evidence).

Compared with aspirin NSAIDs may be more effective at reducing pain compared with aspirin in women with dysmenorrhoea (very low-quality evidence).

Compared with paracetamol NSAIDs may be as effective as paracetamol at reducing pain in women with dysmenorrhoea (very low-quality evidence).

Compared with co-proxamol NSAIDs may be as effective as co-proxamiol at reducing pain in women with dysmenorrhoea (very low-quality evidence).

Compared with TENS The effectiveness of NSAIDs is unclear compared with TENS in women with primary dysmenorrhoea (very low-quality evidence).

Compared with acupressure Ibuprofen is as effective as acupressure at reducing pain in women with dysmenorrhoea (moderate-quality evidence).

Compared with topical heat An unheated topical patch plus ibuprofen may be as effective as topical heat treatment plus placebo (low-quality evidence).

Different NSAIDs compared with each other There may be no significant difference in the effectiveness of different NSAIDs compared with each other at reducing pain after 8–12 hours (very low-quality evidence).

Ibuprofen plus vitamin E compared with ibuprofen alone Vitamin E plus ibuprofen is no more effective at reducing pain compared with ibuprofen alone (moderate-quality evidence).

Restricted activities

Compared with placebo NSAIDs may reduce restriction of daily activities and increase the ability to work compared with placebo (low-quality evidence).

Adverse effects

It remains unclear from direct comparisons which NSAIDs have better safety. The harms of NSAIDs, including the COX-2 inhibitor class, include gastrointestinal ulceration and haemorrhage for traditional NSAIDs and, for at least some of the COX-2 inhibitors, increased cardiovascular risk. Co-proxamol has been withdrawn in some countries because of evidence that fatal toxicity may occur with a small multiple of the normal therapeutic dose and that, therefore, a proportion of fatalities is caused by inadvertent overdose.

For GRADE evaluation of interventions for dysmenorrhoea, see table, p 23 .

Benefits:

NSAIDs versus placebo:

We found one systematic review [13] and two subsequent RCTs . [14] [15] The systematic review (search date 2003) included only double blind RCTs with less than 20% loss to follow up and examined the effects of any NSAIDs (NSAIDs; excluding cyclo-oxygenase-2 [COX-2] selective inhibitors). [13] It found that, with the exception of niflumic acid, each NSAID significantly relieved moderate to severe pain compared with placebo (14 RCTs, 599 women; RR 3.43, 95% CI 2.70 to 4.35). [13] It also found that NSAIDs significantly reduced restriction of daily activities (3 RCTs, 216 women; RR 0.65, 95% CI 0.51 to 0.83), absence from work or school (4 RCTs, 229 women; RR 0.46, 95% CI 0.34 to 0.61), and the need for additional analgesia (10 RCTs, 667 women; RR 0.57, 95% CI 0.47 to 0.69; see comment below) compared with placebo. [13] The first subsequent RCT (104 women, crossover design; see comment below) compared ibuprofen arginate 200 or 400 mg, ibuprofen 200 or 400 mg, and placebo over five menstrual cycles. [14] It found that ibuprofen arginate 200 or 400 mg and ibuprofen 400 mg significantly relieved pain compared with placebo (TOTPAR scores at 8 and 12 hours, time to pain relief, and time to remedication; $P < 0.05$). The second subsequent RCT (crossover design, 73 women with moderate to severe primary dysmenorrhoea) compared the COX-2 selective NSAID etoricoxib 120 mg, naproxen sodium 550 mg, and placebo taken at the onset of painful menses. [15] It found that both etoricoxib and naproxen sodium significantly reduced pain compared with placebo over 8 hours (TOPAR-8 score: 20.0 with etoricoxib *v* 21.5 with naproxen sodium *v* 12.6 with placebo, $P < 0.001$ for each active treatment *v* placebo).

Comparison of NSAIDs:

We found one systematic review [13] and three subsequent RCTs . [14] [15] [16] The systematic review identified 26 RCTs, which compared different NSAIDs, [13] but only three reported data that were suitable for meta-analysis. These RCTs compared mefenamic acid (500 mg 3 times daily) versus tolfenamic acid (200 mg 3 times daily), diclofenac (50 mg up to 3 times daily as required) versus nimesulide (100 mg up to 3 times daily as required), and naproxen sodium (up to a maximum daily dose of 660 mg) versus ibuprofen (up to a maximum daily dose of 1200 mg). The review found no significant difference in pain relief between treatments (mefenamic acid *v* tolfenamic acid, 1 RCT, 73 women: WMD +0.23, 95% CI –0.64 to +1.10; diclofenac *v* nimesulide, 1 RCT, 304 women: OR 0.69, 95% CI 0.38 to 1.25; ibuprofen *v* naproxen, 1 RCT, 81 women: OR 0.57, 95% CI 0.23 to 1.38). The first subsequent RCT (104 women, crossover design; see comment below) compared ibuprofen arginate 200 or 400 mg, conventional ibuprofen 200 or 400 mg, and placebo over five menstrual cycles. [14] It found that higher dose ibuprofen arginate relieved pain significantly faster than conventional ibuprofen at either dose ($P < 0.05$ for TOTPAR scores at 8 and 12 hours, time to pain relief: 56 minutes with ibuprofen arginate *v* 90 minutes with ibuprofen 200 mg *v* 86 minutes with ibuprofen 400 mg; $P < 0.05$ for both comparisons). The RCT found no significant difference between all active treatments in time to remedication ($P > 0.05$). The second subsequent RCT (crossover design, 73 women with moderate to severe primary dysmenorrhoea; see above) found no significant difference in pain between etoricoxib and naproxen over 8 hours (mean TOPAR-8 score: 20.0 units with etoricoxib *v* 21.5 units with naproxen sodium; $P = 0.326$). [15] The third subsequent RCT (337 women with primary dysmenorrhoea) compared three interventions: meloxicam 7.5 mg daily, meloxicam 15 mg daily, and mefenamic acid (500 mg 3 times/day). It found no significant difference in patient-assessed efficacy among groups over 3–5 days and three menstrual cycles (proportion of women who rated treatment as good: 43/100 [43%] with meloxicam 7.5 mg *v* 44/104 [42%] with meloxicam 15 mg *v* 37/104 [35%] with mefenamic acid; P value for all groups *v* each other reported as not significant, figures not reported). [16]

NSAIDs versus aspirin or paracetamol:

We found two systematic reviews (search dates 1997 [17] and 2003 [13]). The second review identified no RCTs comparing NSAIDs versus aspirin that were suitable for meta-analysis. The reviews identified two RCTs, which found no significant difference in pain relief between an NSAID (ibuprofen or naproxen) and paracetamol (see table 2, p 22).

NSAIDs versus co-proxamol:

We found one systematic review (search date 1997, 3 RCTs [18] [19] [20]), which compared NSAIDs versus co-proxamol. [17] The first of these RCTs (56 women) compared mefenamic acid (500 mg 3 times daily) versus co-proxamol (650 mg/65 mg 3 times daily). [18] It found that mefenamic acid significantly reduced dysmenorrhoea related symptoms compared with co-proxamol (see table 2, p 22). Mefenamic acid also reduced the need for additional medication compared with co-proxamol (mean number of tablets of additional medication: 2.6 with mefenamic acid *v* 6.8 with co-proxamol; significance assessment not reported). The RCT found similar rates of absence from work or school between treatments (total days of absence: 10.50 with mefenamic acid *v* 15.25 with co-proxamol; significance assessment not reported). Two RCTs (98 women) identified by the review compared naproxen (275 mg 3 times daily) versus co-proxamol (650 mg/65 mg 3 times daily). Neither RCT found a significant difference in pain severity (see table 2, p 22). [19] [20]

NSAIDs versus TENS:
See benefits of TENS, p 10 .

Ibuprofen versus ibuprofen plus vitamin E:
See benefits of vitamin E, p 11 .

Ibuprofen versus acupressure:
See benefits of acupressure, p 6 .

Ibuprofen versus topical heat:
See benefits of topical heat, p 9 .

Harms:

The harms of NSAIDs, including the COX-2 inhibitor class, are considered in detail elsewhere in *BMJ Clinical Evidence* (see review on NSAIDs), and include gastrointestinal ulceration and haemorrhage for traditional NSAIDs and, for at least some of the COX-2 inhibitors, increased cardiovascular risk. Co-proxamol has been withdrawn in some countries owing to evidence that fatal toxicity may occur with a small multiple of the normal therapeutic dose and, therefore, a proportion of fatalities is caused by inadvertent overdose.

NSAIDs versus placebo:
The most commonly reported adverse effects in the RCTs identified by the first review were mild neurological and gastrointestinal symptoms. [13] The review found no significant difference between any particular NSAID and placebo in the frequency of adverse effects. However, pooled results showed that, overall, NSAIDs significantly increased adverse effects compared with placebo (RR 1.29, 95% CI 1.05 to 1.59). The first subsequent RCT found no significant difference between ibuprofen arginate, ibuprofen, or placebo in the incidence of headache, nausea, and dizziness (reported as not significant, figures not reported). [14] No participants discontinued treatment because of adverse effects. The fourth subsequent RCT found similar rates of adverse effects with active treatments and placebo. [15] The most common adverse effects were headache and nausea. No serious adverse experiences were reported (incidence of adverse effects: 12% with etoricoxib *v* 25% with naproxen sodium *v* 15% with placebo; headache: 1.5% with etoricoxib *v* 7.5% with naproxen sodium *v* 4.5% with placebo; nausea: 3% with etoricoxib *v* 3% with naproxen sodium *v* 1.5% with placebo, significance assessment not performed).

Comparison of NSAIDs:
The first systematic review [13] found no significant difference in rates of adverse effects between different NSAIDS in any of the RCTs identified (all adverse effects: ibuprofen *v* fenoprofen, 1 RCT, 111 women: OR 1.51, 95% CI 0.72 to 3.18; naproxen *v* other NSAIDs, 2 RCTs, 323 women: OR 1.09, 95% CI 0.54 to 2.22). The first subsequent RCT (described above) found no significant difference between ibuprofen arginate, ibuprofen, or placebo in the incidence of headache, nausea, and dizziness (reported as not significant, figures not reported). [14] The second subsequent RCT found a similar incidence of clinical adverse effects between etoricoxib and naproxen sodium. The most common adverse effects were headache and nausea. No serious adverse experiences were found (incidence of clinical adverse effects: 12% with etoricoxib *v* 25% with naproxen sodium; headache: 1.5% with etoricoxib *v* 7.5% with naproxen sodium; nausea: 3% with etoricoxib *v* 3% with naproxen sodium, significance assessments not reported). [15] The third subsequent RCT found that significantly more women had adverse effects, primarily gastrointestinal, with mefenamic acid than with meloxicam at either dose (25/110 [23%] with mefenamic acid *v* 11/113 [10%] with meloxicam 7.5 mg *v* 13/114 [11%] with meloxicam 15 mg; P value reported as significant, figures not reported). [16]

NSAIDs versus aspirin or paracetamol:
The reviews found no significant difference in gastrointestinal adverse effects or nervous system adverse effects between paracetamol and naproxen [13] [17] or ibuprofen (see table 2, p 22).

NSAIDs versus co-proxamol:
The review found that co-proxamol was associated with significantly more adverse effects than naproxen (see table 2, p 22). [17]

NSAIDs versus TENS:
See harms of TENS, p 10 .

Ibuprofen versus ibuprofen plus vitamin E:
See harms of vitamin E, p 11 .

Ibuprofen versus acupressure:
See harms of acupuncture, p 12 .

Ibuprofen versus topical heat:
See harms of topical heat, p 9 .

Comment:

All RCTs identified used oral treatment. [13] [14] [15] [16] In the first systematic review, [13] only five of the included RCTs clearly described methods of randomisation and allocation concealment. At least half of the RCTs were co-authored or financially supported by pharmaceutical company associates; it was unclear how the others were funded, with the exception of a single study that reported receipt of a grant from an academic institution. The measurement and reporting of adverse effects by individual RCTs was generally poor, even taking into account the challenge of distinguishing between dysmenorrhoeic symptoms and medication effects. Methods of collecting this information varied: about a third of the RCTs described the use of prospective self report forms or diaries, but another third assessed adverse effects retrospectively (at follow up appointments), and the others were not specific about their methods. In some cases, the adverse effects recorded were those deemed by the study investigator to be medication related. Few RCTs provided adverse effect data suitable for meta-analysis, and many provided no numerical data at all. Despite the large number of included trials, it was not clear which NSAIDs were most effective for dysmenorrhoea. This was because most of the trials were relatively small, they covered a large number of different comparisons, and few of them provided data suitable for meta-analysis (only 14/36 RCTs were included in meta-analyses). Of the 24 additional comparisons of 12 different NSAIDs versus placebo, 19 found that NSAIDs significantly relieved pain ($P < 0.05$), three found no significant difference (aspirin, diclofenac, and ibuprofen), and two did not report statistical results. The meta-analytical results for assessing restriction of daily activities and the need for additional analgesia [13] included data from one arm of an RCT (85 women; 4 treatment arms), which compared aspirin versus placebo. However, these data are unlikely to affect the applicability of the results. The first subsequent RCT used a crossover design without a washout period and was co-authored by a pharmaceutical company. [14]

Clinical guide:
NSAIDs can be given as suppositories, which seem to have a similar effect on overall pain relief but less effect than oral treatment on spasmodic pain. [21]

OPTION ACUPRESSURE New

Pain
Compared with usual care or sham acupressure Acupressure reduces pain compared wtih waiting list controls or sham acupressure after 2–3 months (moderate-quality evidence).

Compared with ibuprofen Acupressure is as effective as ibuprofen at reducing pain in women with dysmenorrhoea (moderate-quality evidence).

For GRADE evaluation of interventions for dysmenorrhoea, see table, p 23 .

Benefits:

We found two RCTs comparing acupressure for the treatment of primary dysmenorrhoea. [22] [23] The first RCT compared a specially designed cotton acupressure brief containing 10 latex foam pads fixed over lower abdominal and lower back acupressure points versus a waiting list control, who received usual care. [22] The acupressure brief was worn on the first 3 days of menses, for two menstrual cycles, for as long as possible without discomfort. The RCT found the acupressure briefs significantly reduced the mean scores for “worst” menstrual pain (61 women with primary dysmenorrhoea, aged 20–40 years; pain measured using the Descriptive Numeric Rating Scale of Pain Intensity and Distress Inventory, 11 point scale, where 0 = no pain and 10 = worst pain imaginable; mean score: 3.9 with acupressure briefs *v* 7.3 with control; $P < 0.001$), and reduced menstrual symptoms (Menstrual Pain Symptom Intensity Scale, where 0 = no pain and 12 = most severe pain; mean score: 2.9 with acupressure briefs *v* 7.1 with control; $P < 0.05$) compared with control after two menstrual cycles. The RCT also found acupressure briefs increased the proportion of women experiencing a clinically significant drop in pain scores after two menstrual cycles (defined in at least a 25% reduction in pain score; AR: 25/28 [89%] with acupressure briefs *v* 2/26 [8%] with control; $P < 0.05$). [22] The second RCT compared three treatments: self administered acupressure, ibuprofen, and placebo acupressure (using incorrect pressure points) for three menstrual cycles. [23] It found that acupressure and ibuprofen significantly increased the number of women reporting no pain after 3 months compared with placebo, but found no significant difference between acupressure and ibuprofen (216 women with primary dysmenorrhoea; aged 14–18 years; 4 point visual analogue pain scale, where 0 = no pain and 3 = most pain; AR for no pain: 50% with acupressure *v* 36% with ibuprofen *v* 18% with placebo; difference between active treatments and placebo reported as significant; difference between acupressure and ibuprofen reported as not significant, P values not reported).

Harms: Four women (14.3%) in the first RCT found the discomfort from wearing the acupressure briefs so great that they did not use them in the second menstrual cycle. [22] The second RCT did not report on adverse events. [23]

Comment: None.

OPTION ASPIRIN, PARACETAMOL, AND COMPOUND ANALGESICS

Pain

Aspirin compared with placebo Aspirin may reduce pain in women with dysmenorrhoea (low-quality evidence).

Paracetamol compared with placebo Paracetamol may be no more effective than placebo at reducing pain (low-quality evidence).

Co-proxamol compared with placebo Co-proxamol may be more effective than placebo at reducing pain (low-quality evidence).

Aspirin compared with paracetamol Aspirin may be as effective as paracetamol at reducing pain (low-quality evidence).

Aspirin compared with NSAIDs Aspirin may be less effective at reducing pain compared with NSAIDs in women with dysmenorrhoea (very low-quality evidence).

Paracetamol compared with NSAIDs Paracetamol may be as effective as NSAIDs at reducing pain in women with dysmenorrhoea (very low-quality evidence).

Co-proxamol compared with NSAIDs Co-proxamol may be as effective as NSAIDs at reducing pain in women with dysmenorrhoea (very low-quality evidence).

Paracetamol compared with topical heat treatment Paracetamol is less effective at reducing pain in women with primary dysmenorrhoea compared with topical heat treatment (moderate-quality evidence).

Adverse effects

Co-proxamol has been withdrawn in some countries owing to evidence that fatal toxicity may occur with a small multiple of the normal therapeutic dose and that, therefore, a proportion of fatalities is caused by inadvertent overdose.

For GRADE evaluation of interventions for dysmenorrhoea, see table, p 23 .

Benefits:

Aspirin versus placebo:
We found two systematic reviews. [13] [17] The first review (search date 1997, 8 RCTs, 486 women) found that aspirin (650 mg 4 times daily) significantly increased the proportion of women with pain relief compared with placebo (proportion of women with at least moderate pain relief, see table 2, p 22). It found no significant difference between aspirin and placebo in the need for additional medication (3 RCTs: RR 0.79, 95% CI 0.58 to 1.08), restriction of daily activity (3 RCTs: RR 0.82, 95% CI 0.64 to 1.04), and absence from work (1 RCT: RR 1.28, 95% CI 0.24 to 6.76). [17] The second systematic review (search date 2003, 2 RCTs, 143 women) included only double blind RCTs with less than 20% loss to follow up. [13] It found no RCTs for which the results were suitable for quantitative analysis of effects on pain relief. However, it found no significant difference between aspirin (650 mg daily during menses) and placebo in the need for additional medication (1 RCT, 36 women; RR 0.86, 95% CI 0.46 to 1.60).

Paracetamol versus placebo:
We found one systematic review (search date 1997, 1 RCT, 35 women). [17] It found no significant difference between paracetamol (500 mg 4 times daily) and placebo in pain relief (see table 2, p 22).

Co-proxamol versus placebo:
We found one systematic review (search date 1997, 1 RCT, 72 women). [17] It found that co-proxamol significantly increased the proportion of women with at least moderate pain relief compared with placebo (see table 2, p 22).

Paracetamol versus aspirin:
We found one systematic review (search date 1997, 1 RCT, 35 women). [17] It found no significant difference in pain relief between aspirin (500 mg 4 times daily) and paracetamol (500 mg 4 times daily, see table 2, p 22).

Aspirin or paracetamol or co-proxamol versus NSAIDs:
See benefits of NSAIDs, p 3 .

Paracetamol versus topical heat:
See benefits of topical heat, p 9 .

Harms:

Aspirin versus placebo:
The first systematic review found no significant difference in adverse effects between aspirin and placebo (see table 2, p 22). [17] It also found no significant difference in rates of nausea (RR 1.66, 95% CI 0.59 to 4.67), dizziness (RR 1.29, 95% CI 0.28 to 5.89), and headache (RR 0.60, 95% CI 0.18 to 2.04) between aspirin and placebo. The second systematic review also found no significant difference in adverse effects between aspirin and placebo (see table 2, p 22). [13] It also found no significant difference in rates of gastrointestinal adverse effects (OR 1.91, 95% CI 0.39 to 9.26) and nervous system adverse effects (OR 3.66, 95% 0.75 to 17.71) between aspirin and placebo.

Paracetamol versus placebo:
The systematic review found no significant difference between paracetamol and placebo in the frequency of adverse effects (any adverse effect for paracetamol *v* placebo [see table 2, p 22]). [17]

Co-proxamol versus placebo:
The review did not report on adverse effects for this comparison. [17] Co-proxamol has been withdrawn in some countries owing to evidence that fatal toxicity may occur with a small multiple of the normal therapeutic dose and, therefore, a proportion of fatalities are caused by inadvertent overdose.

Paracetamol versus aspirin:
The review did not report on adverse effects for this comparison. [17]

Aspirin or paracetamol or co-proxamol versus NSAIDs:
See harms of NSAIDs, p 3 .

Paracetamol versus topical heat:
See harms of topical heat, p 9 .

Comment:

Most RCTs included in the first systematic review were short (usually only 1 menstrual cycle on each treatment), small, and used a crossover design without a washout period. [17] All of the RCTs (except one RCT comparing co-proxamol *v* naproxen) used double blinding. All of the RCTs used oral administration of treatment in the form of tablets or capsules. Negative RCTs may have been too small to detect clinically important differences between aspirin, paracetamol, or compound analgesics and placebo.

OPTION THIAMINE

Pain
Compared with placebo Thiamine seems to be more effective at reducing pain after 60 days compared with placebo in indian adolescent women with primary dysmenorrhoea (moderate-quality evidence).

For GRADE evaluation of interventions for dysmenorrhoea, see table, p 23 .

Benefits:

Thiamine versus placebo:
We found one systematic review (search date 2000, 1 RCT). [24] The RCT identified by the review (crossover design; 556 Indian adolescents attending school) compared thiamine 100 mg daily versus placebo for 3 months. It found that thiamine significantly increased the proportion of women with no pain before crossover after 60 days compared with placebo (142/277 [51%] with thiamine *v* 0/279 [0%] with placebo; NNT 2, 95% CI 2 to 3). After completion of the RCT, 87% of all women experienced no pain. [24]

Harms:

The review gave no information on the adverse effects of thiamine. [24]

Comment:

None.

OPTION TOKI-SHAKUYAKU-SAN (HERBAL REMEDY)

Pain
Compared with placebo Toki-shakuyaku-san may reduce pain after 6 months compared with placebo in women with primary dysmenorrhoea (very low-quality evidence).

For GRADE evaluation of interventions for dysmenorrhoea, see table, p 23 .

Benefits: We found one systematic review (1 RCT, search date 2000, 50 women), which compared herbal and dietary remedies versus placebo. [24] It found that a Japanese herbal remedy (see comment below), toki-shakuyaku-san (2.5 g 3 times daily), significantly reduced pain, as measured by a visual analogue scale after 6 months compared with placebo ($P < 0.005$), and reduced the need for additional medication (diclofenac sodium) ($P < 0.01$; results presented graphically).

Harms: **Toki-shakuyaku-san versus placebo:**
The RCT gave no information on adverse effects. [24]

Comment: Toki-shakuyaku-san is a mixture of six herbs, including angelica and peony root. The allocation method was not clearly described in the RCT. [24] A systematic review of Chinese medicinal herbs for primary dysmenorrhoea is underway. [25]

OPTION TOPICAL HEAT (ABOUT 39 °C)

Pain

Compared with placebo Topical heat plus placebo tablets may be more effective at reducing pain compared with an unheated patch plus placebo in women with primary dysmenorrhoea (low-quality evidence).

Compared with NSAIDs Topical heat treatment plus placebo may be as effective as unheated topical patch plus ibuprofen (low-quality evidence).

Compared with paracetamol Topical heat treatment is more effective than paracetamol at reducing pain in women with primary dysmenorrhoea (moderate-quality evidence).

For GRADE evaluation of interventions for dysmenorrhoea, see table, p 23 .

Benefits: **Topical heat versus placebo, paracetamol, or ibuprofen:**
We found no systematic review but found two RCTs. [26] [27] The first was an efficacy RCT (84 women with moderate or greater pain in at least 4 of their last 6 cycles who experienced pain relief with non-prescription analgesics and had a history consistent with a diagnosis of primary dysmenorrhoea) of topically applied heat, which used a double dummy design with a heated or unheated patch plus oral ibuprofen or placebo. [26] An abdominal patch (heated to 38.9 °C *v* unheated) was applied for about 12 hours daily for 2 days from the start of menses. In addition, oral medication (placebo *v* ibuprofen 400 mg) was given three times daily for 2 days. There were four treatment groups: heated patch plus placebo; heated patch plus ibuprofen; unheated patch plus placebo; and unheated patch plus ibuprofen. Pain relief was measured on a scale from 0 (no relief) to 5 (complete relief). After 2 days of treatment, significant pain relief compared with the unheated patch plus placebo group (mean pain relief score: 1.95) was obtained with the heated patch plus placebo (mean pain relief score: 3.27; $P < 0.001$), with the heated patch plus ibuprofen (mean pain relief score: 3.55; $P < 0.001$), and with the unheated patch plus ibuprofen (mean pain relief score: 3.07; $P = 0.001$). There was no significant difference in pain relief between the heated patch plus ibuprofen and the unheated patch plus ibuprofen groups ($P = 0.09$). However, the "time to noticeable pain relief" was significantly shorter for the heated patch plus ibuprofen compared with the unheated patch plus ibuprofen group (median: 1.50 hours with the heated patch plus ibuprofen *v* 2.79 hours with the unheated patch plus ibuprofen; $P = 0.01$; no further data provided). Pain intensity was measured on a 100 point numerical scale ranging from 0 (no pain) to 100 (worst possible pain). After 2 days of treatment, all treatment groups had a significant reduction in pain intensity compared with unheated patch plus placebo (mean pain intensity reduction: 40.4 with heated patch plus placebo *v* 39.0 with unheated patch plus ibuprofen *v* 43.8 with heated patch plus ibuprofen *v* 21.9 with unheated patch plus placebo; $P < 0.003$ for individual group comparisons *v* unheated patch plus placebo). There was no significant difference between heated patch plus placebo and unheated patch plus ibuprofen in the reduction in pain intensity at 2 days ($P = 0.8$). [26] The second RCT (344 women with primary dysmenorrhoea) compared four interventions: abdominal heat wrap (heated to 40 °C for 8 hours from the first morning after the start of menses), unheated abdominal wrap (for same time period), high dose paracetamol (1000 mg 4 times a day), and placebo. [27] Pain relief was measured on a scale from 1 to 6, which was converted to a TOTPAR score. The RCT found that the heated wrap significantly reduced pain after 8 hours of treatment compared with paracetamol (mean score: 2.48 with heated wrap *v* 2.17 with paracetamol; $P = 0.015$). No data were reported for the placebo groups.

Harms: The first RCT found that women using a heated patch were more likely to report pinkness or redness of the skin than those using an unheated patch at the end of day 2 after 12 continuous hours of use (23/40 [58%] with a heated patch *v* 5/41 [12%] with an unheated patch; OR 9.74, 95% CI 3.16 to 30.04). [26] All women reported normal skin 3–7 days after starting treatment. The second RCT found that two women using abdominal heat wrap reported adverse effects (conjunctivitis and pink skin), four women taking paracetamol reported adverse effects (headache, rhinitis, upper respira-

tory infection, and anxiety), and one woman in the placebo group reported headaches. [27] The RCT stated that all adverse effects other than pink skin were most likely unrelated to the study interventions; pink skin resolved within 1 hour of removing the heated wrap.

Comment:

Clinical guide:
Participants in the first RCT included volunteer women. [26] Dysmenorrhoea in these women may have a different pattern and response to treatment than dysmenorrhoea in women seeking health care.

OPTION TENS

Pain
High-frequency TENS compared with placebo TENS High-frequency TENS reduces pain compared with placebo TENS (moderate-quality evidence).

Low-frequency TENS compared with placebo TENS We don't know whether low-frequency TENS reduces pain compared with placebo TENS (low-quality evidence).

Compared with placebo tablets We don't know whether low-frequency TENS reduces pain compared with placebo tablets (low-quality evidence).

High-frequency TENS compared with low-frequency TENS We don't know whether high-frequency TENS reduces pain compared with low-frequency TENS (low-quality evidence).

Compared with NSAIDs The effectiveness of TENS is unclear compared with NSAIDs in women with primary dysmenorrhoea (very low-quality evidence).

For GRADE evaluation of interventions for dysmenorrhoea, see table, p 23 .

Benefits:

We found one systematic review including women with primary dysmenorrhoea (search date 2001, 8 RCTs, 172 women). [28]

High frequency TENS versus placebo TENS:
The review found that high frequency TENS significantly increased pain relief compared with placebo TENS, as measured by subjective assessment or by a visual analogue scale (pain relief by subjective assessment, 2 RCTs, 53 women: OR 7.2, 95% CI 3.1 to 16.5; pain relief by visual analogue scale range 0 [no pain relief] to 100 [total pain relief], 1 RCT, 18 women: WMD 45.0 units, 95% CI 22.5 units to 67.5 units). The review found no significant difference in the proportion of women needing additional analgesics between high frequency TENS and placebo TENS (1 RCT, 64 women: OR 0.3, 95% CI 0.1 to 1.1). It also found no significant difference in the number of analgesic tablets taken each day between high frequency TENS and placebo TENS (1 RCT, 24 women, mean: 6.92 tablets with high frequency TENS *v* 6.78 tablets with placebo; WMD +0.1 tablets, 95% CI –2.1 tablets to +2.4 tablets). It found no significant difference between high frequency TENS and placebo TENS in absence from work or school, as measured by the number of lost hours each menstrual cycle (1 RCT, 24 women: WMD +0.04 hours, 95% CI –0.4 hours to +0.5 hours). [28]

Low frequency TENS versus placebo TENS:
The review found no significant difference in pain relief between low frequency TENS and placebo TENS (pain relief by subjective assessment, 2 RCTs, 29 women: OR 1.3, 95% CI 0.4 to 4.1; pain relief by visual analogue scale 0–100, 1 RCT, 18 women: WMD +24.1 units, 95% CI –2.9 units to +51.1 units). One additional RCT (24 women), which could not be included in the meta-analysis because of the way in which the results were reported, found that pain relief was significantly increased by low frequency TENS compared with placebo TENS ($P < 0.05$). Low frequency TENS reduced the number of additional tablets of analgesic used compared with placebo TENS (1 RCT, 24 women: WMD –3.1 tablets, 95% CI –5.5 tablets to –0.7 tablets). However, there was no significant difference between the two groups for hours of absence from work or school (1 RCT, 24 women: WMD –0.2 hours, 95% CI –0.6 hours to +0.2 hours). [28]

Low frequency TENS versus placebo tablets:
The review found no significant difference in pain relief between low frequency TENS and placebo tablets (1 RCT, 21 women: OR 2.9, 95% CI 0.4 to 24.4). One additional RCT (20 women), which could not be included in the meta-analysis, found that low frequency TENS increased pain relief compared with placebo tablets ($P < 0.05$). [28]

High frequency TENS versus low frequency TENS:
The review found that high frequency TENS was significantly more effective than low frequency TENS for pain relief measured by subjective assessment (1 RCT, 21 women: OR 3.9, 95% CI 1.1 to 13.0), but not for pain relief measured with a visual analogue scale (1 RCT, 18 women: WMD +21 units, 95% CI –4.4 units to +46 units). One additional RCT, which could not be included in the meta-analysis, found that low frequency TENS significantly reduced pain compared with high frequency TENS ($P < 0.05$). The review found that low frequency TENS significantly reduced the number of additional analgesic tablets taken compared with high frequency TENS (WMD 3.2 tablets, 95% CI 0.5 tablets to 5.9 tablets). There was no significant difference between the two groups in absence from work or school (WMD +0.2 hours, 95% CI –0.2 hours to +0.6 hours). [28]

High frequency TENS versus NSAIDs:
The review [28] identified two RCTs, [29] [30] which compared TENS versus NSAIDs. The first RCT (crossover design, 32 women) compared high frequency TENS, ibuprofen, and placebo. It found that high frequency TENS was significantly less effective than ibuprofen in achieving pain relief (proportion of women experiencing pain relief: 14/32 [44%] with TENS *v* 24/32 [75%] with ibuprofen; OR 0.26, 95% CI 0.09 to 0.75). [29] The second RCT (open label, crossover design, 12 women) found no significant difference between naproxen and high frequency/high intensity TENS in pain relief (data presented graphically, and significance assessment not performed). [30]

Harms:

High frequency TENS versus placebo TENS:
The adverse effects of muscle vibrations, tightness, headaches, and slight burning or redness after use were experienced by four women having high frequency TENS and none having placebo (RR 9.00, 95% CI 0.50 to 160.59). [28]

Low frequency TENS versus placebo tablets:
There were no reported adverse effects from low frequency TENS or placebo TENS.

High frequency TENS versus NSAIDs:
The second RCT [30] identified by the review, which compared high frequency TENS versus naproxen, reported an increase in the number of adverse effects experienced by women with high frequency TENS compared with naproxen (OR 26.7, 95% CI 5.5 to 130.9). [28] Ten women (83%) experienced pain from TENS treatment, whereas there were no reported adverse effects with naproxen. The women who reported pain from TENS stated that they were prepared to accept the short term pain from the treatment in return for relief of dysmenorrhoea. [28] [30]

Comment: None.

OPTION VITAMIN E

Pain
Compared with placebo Vitamin E tablets reduce pain compared with placebo at 2–4 months in women with primary dysmenorrhoea (moderate-quality evidence).

Vitamin E plus ibuprofen compared with ibuprofen alone Vitamin E plus ibuprofen is no more effective at reducing pain compared with ibuprofen alone (moderate-quality evidence).

For GRADE evaluation of interventions for dysmenorrhoea, **see table, p 23 .**

Benefits:

Vitamin E versus placebo:
We found one systematic review (search date 2002, 2 RCTs) [31] and one subsequent RCT. [32] The first RCT identified by the review (100 women aged 16–18 years) compared vitamin E (500 units/day [about 333 mg], from 2 days before expected menses until the third day of menses) versus placebo for 2 months. It found that vitamin E significantly reduced pain compared with placebo (median 10 cm visual analogue scale pain scores: 3.5 cm with vitamin E *v* 4.3 cm with placebo; $P = 0.02$). [33] The second RCT identified by the review (100 women aged 18–21 years) compared vitamin E (500 mg 3 times daily from 10 days before expected menses until the fourth day of menses) versus placebo for 3 months. It found that vitamin E increased pain relief compared with placebo (proportion with improvement in pain: 34/50 [68%] with vitamin E *v* 9/50 [18%] with placebo; significance assessment not performed). [31] The subsequent RCT (278 girls aged 15–17 years with primary dysmenorrhoea) compared vitamin E (200 units/day, from 2 days before expected menses until the third day of menses) versus placebo for four menstrual cycles. [32] It found that vitamin E significantly reduced pain severity and duration at 4 months compared with placebo (pain severity on a score from 0–10, where 0–3.0 = mild, 3.1–6.0 = moderate, and 6.1–10.0 = severe: median visual analogue scale score: 0.5 with vitamin E *v* 6.0 with placebo; $P < 0.001$; mean pain duration: 1.6 hours with vitamin E *v* 17.0 hours with placebo: $P < 0.0001$). [32]

Vitamin E plus ibuprofen versus ibuprofen alone:
We found one systematic review (search date 2000, 1 RCT). [24] The RCT identified by the review (crossover design, 50 women) compared vitamin E (100 mg/day for 20 days before menses) plus ibuprofen (400 mg 3 times daily at the onset of painful menstruation) versus ibuprofen alone (400 mg 3 times daily at the onset of pain). It found no significant difference between vitamin E plus ibuprofen and ibuprofen alone in pain relief (proportion of women experiencing pain relief: 23/26 [88%] with vitamin E plus ibuprofen *v* 17/24 [71%] with ibuprofen alone; RR 1.25, 95% CI 0.93 to 1.67). [24]

Harms: The RCTs gave no information on adverse effects. [24] [31] [32]

Comment: None.

OPTION ACUPUNCTURE

Pain
Compared with placebo acupuncture or no treatment Acupuncture may reduce pain at 3 months compared with placebo acupuncture, monthly medical visits or no treatment (low-quality evidence).

For GRADE evaluation of interventions for dysmenorrhoea, see table, p 23 .

Benefits: We found one systematic review of acupuncture for primary dysmenorrhoea (search date 2001, 1 RCT, 43 women). [28] The RCT identified by the systematic review compared weekly acupuncture (30–40 minutes) for 3 weeks of a menstrual cycle for a total of 3 months (equivalent to three menstrual cycles) versus three other treatments: placebo acupuncture; monthly medical visits; or no medical visits. Outcomes were assessed after 3 months using non-validated pain scales and symptom questionnaires, and improvement was defined as a reduction in pain by more than half the admission score. It found that acupuncture significantly increased the proportion of women with reduced pain compared with other treatments (proportion of women with reduction in pain of more than half the admission score: 10/11 [91%] with acupuncture *v* 4/11 [36%] with placebo acupuncture *v* 1/10 [10%] with monthly medical visits *v* 2/11 [18%] with no medical treatment; $P < 0.05$ for acupuncture *v* all other treatments).

Harms: The RCT identified by the review gave no information on adverse effects. [34]

Comment: The scale used to assess outcomes in the RCT identified by the review does not seem to be validated. [28] We found no evidence of statistical adjustment for multiple comparisons (such as Bonferroni's correction) in the published paper. [34]

OPTION BEHAVIOURAL INTERVENTIONS

Pain
Relaxation treatment compared with waiting list control Relaxation treatment may reduce symptoms of dysmenorrhoea compared with waiting list control in women with primary dysmenorrhoea (low-quality evidence).

Exercise compared with no exercise Regular aerobic exercise may reduce pain at 3 months compared with a sedentary lifestyle (very low-quality evidence).

For GRADE evaluation of interventions for dysmenorrhoea, see table, p 23 .

Benefits: We found one systematic review of complementary and alternative medicine (search date 2002) including behavioural interventions. [35]

Relaxation treatment:
The systematic review (search date 2002) found no RCTs. [35] We found one additional RCT (69 women with congestive or spasmodic dysmenorrhoea), which compared relaxation treatment plus positive imagery regarding menstruation, self directed group discussion about menstruation, and waiting list control. The groups were divided into women with congestive or spasmodic dysmenorrhoea using the Menstrual Symptom Questionnaire. It found that, in women with spasmodic or congestive dysmenorrhoea, relaxation treatment significantly improved dysmenorrhoeic symptoms compared with waiting list control ($P < 0.01$). However, it found that only the women with spasmodic dysmenorrhoea experienced significantly less pain with relaxation compared with group discussion or waiting list control ($P < 0.001$). [36]

Exercise:
The systematic review (search date 2002), [35] identified one RCT which met our inclusion criteria. [35] The RCT (36 women) compared a training group that participated in 30 minutes of aerobic

exercise 3 days a week for 3 months versus a sedentary control group. [37] It found that aerobic exercise significantly lowered Menstrual Distress Questionnaire scores (P < 0.05; absolute results presented graphically).

Harms: The review [35] and individual RCTs [36] [37] gave no information on adverse effects.

Comment: In the RCT on relaxation, spasmodic dysmenorrhoea was defined as spasms of pain mainly in the abdomen, and congestive dysmenorrhoea was defined as a dull aching pain in the lower abdomen and other areas of the body. [36] However, the classification of dysmenorrhoea into spasmodic and congestive categories is no longer commonly used and has little meaning. [37] The RCT (36 women) that compared aerobic exercise with a sedentary control group analysed results for the 26 women (72%) who completed the trial (11 in the exercise group and 15 in the control group). [37] The systematic review included three additional studies comparing different types of exercise that it described as RCTs; however, there was no mention of randomisation in the original publications. [35] Therefore, we have not included these studies. A systematic review of behavioural interventions is underway (Proctor M, personal communication, 2006).

OPTION COMBINED ORAL CONTRACEPTIVES

Pain

Compared with placebo Combined oral contraceptives may be no more effective than placebo at reducing pain in women with primary dysmenorrhoea at 1–3 months (very low-quality evidence).

For GRADE evaluation of interventions for dysmenorrhoea, see table, p 23 .

Benefits: We found one systematic review of combined oral contraceptives for primary dysmenorrhoea (search date 1999, 5 RCTs, 379 women) [38] and two subsequent RCTs. [39] [40] The systematic review found no significant difference in pain relief at 1–3 months between medium dose oestrogen (> 35 µg) plus first or second generation progestogens and placebo (4 RCTs, 320 women; RR 1.40, 95% CI 0.58 to 3.42; see comment below). [38] It found that combined oral contraceptives reduced the proportion of women absent from work or school compared with placebo but the difference was of borderline significance so its clinical importance is unclear (1 RCT, 89 women: 19/49 [39%] with contraceptives *v* 24/40 [60%] with placebo; RR 0.65, 95% CI 0.42 to 1.00). [38] The first subsequent RCT (77 women) compared a low dose combined oral contraceptive containing desogestrel (a third generation progestogen) plus a low dose of ethinyl estradiol versus placebo for four consecutive monthly cycles. [39] It found that the combined oral contraceptive significantly reduced the severity of menstrual cramping compared with placebo (mean reduction of score for cramping on the Menstrual Distress Questionnaire: 1.4 with combined oral contraceptive *v* 0.3 with placebo; P < 0.01). It found no significant difference in overall menstrual pain between combined oral contraceptive and placebo, although women taking combined oral contraceptive had less pain (mean reduction of score on the Menstrual Distress Questionnaire: 13.7 with combined oral contraceptive *v* 6.2 with placebo; P = 0.074). The RCT found no significant difference between the combined oral contraceptive and placebo in the proportion of women absent from work or school (reported as not significant, figures not reported, absolute results presented graphically). [39] The second subsequent RCT compared a low dose combined oral contraceptive containing levonorgestrel (a second generation progestogen; 100 µg) plus ethinyl estradiol (20 µg) versus placebo for three consecutive monthly cycles. [40] The RCT found that combined oral contraceptive significantly improved pain scores (Moos Menstrual Distress Questionnaire: 6 items; score range from 0–24, where 0 = no pain to 24 = most severe pain) compared with placebo at 3 months (76 adolescent girls aged less-than or equal to 19 years with primary dysmenorrhoea; mean pain scores: 3.1 with combined oral contraceptive *v* 5.8 with placebo; mean difference: –2.70, 95% CI –4.53 to +0.88; P = 0.004). It also found that combined oral contraceptives reduced participant-rated "worst pain" score compared with placebo (mean pain rating: 3.7 with combined oral contraceptive *v* 5.4 with placebo; P = 0.02) and pain medication use (mean pain pills used: 1.3 with combined oral contraceptive *v* 3.7 with placebo; P = 0.05). However, the RCT found no significant difference between the combined oral contraceptive and placebo for the outcomes of days of any pain, days of severe pain, and hours of pain on the worst day (results displayed graphically; P values reported as not significant).

Harms: The review found no significant difference between combined oral contraceptives and placebo in adverse effects such as nausea, vomiting, depression, and abdominal pain (1 RCT, 89 women: 15/49 [31%] with combined oral contraceptives *v* 8/40 [20%] with placebo; RR 1.53, 95% CI 0.72 to 3.24). [38] The results of two RCTs are difficult to interpret and could not be included in the meta-analysis of adverse effects performed by the review because the RCTs randomised menstrual cycles and not women. [41] [42] One small RCT (18 women) identified by the review that compared combined oral contraceptives versus placebo found that more women receiving combined oral contraceptives experienced breakthrough bleeding (2/12 [17%] with combined oral contraceptives *v* 0/6

[0%] with placebo; significance assessment not performed). [41] Another RCT (59 women) identified by the review found that combined oral contraceptives increased weight gain, nausea, and vomiting compared with placebo (no further data reported). [42] The first subsequent RCT found similar rates of adverse effects such as headache, nausea, abdominal pain, bloating, anxiety, loneliness, weight gain, and acne with a low dose combined oral contraceptive compared with placebo (no further data reported). The most frequently reported adverse effect was headache (9/38 [24%] with combined oral contraceptive *v* 3/35 [9%] with placebo; significance assessment not performed). There were no withdrawals owing to adverse effects in either treatment group. [39] The second subsequent RCT reported no serious adverse effects. [40] There were similar discontinuation rates owing to adverse events such as acne, nausea, and moodiness (2/38 [5%] with combined oral contraceptive *v* 1/38 [3%] with placebo; P value not reported). [40] The RCT did not report any further information on adverse effects.

Comment: Most of the RCTs identified by the systematic review had weak methodology. [38] Because of the small number of included trials and participants, the results of the systematic review are sensitive to the statistical methods of calculation used. One of the RCTs identified by the review could not be included in the meta-analysis because of poor reporting of data. [42] All of the RCTs identified by the review used combined oral contraceptives that are no longer commonly prescribed, so the results may not be applicable to women today, who take different preparations. [38] The review was able to perform a meta-analysis of the pain results from these RCTs because pain data were reported as individual patient data. [38] However, this was not the case for adverse effects, so a meta-analysis of adverse effects could not be performed.

OPTION FISH OIL

Pain

Fish oil compared with placebo Fish oil may be no more effective than placebo at reducing pain in women with dysmenorrhoea at 3 months (very low-quality evidence).

For GRADE evaluation of interventions for dysmenorrhoea, see table, p 23 .

Benefits: **Fish oil versus placebo:**
We found one systematic review (search date 2000, 1 RCT; crossover design; 42 women) [24] and one additional RCT, [43] which compared fish oil versus placebo. The RCT identified by the review compared fish oil capsules with placebo twice daily for 1 month. It found that menstrual symptom scores were significantly lower with fish oil compared with placebo (P = 0.04); however, these results should be interpreted with caution (see comment below). [24] Less additional medication (ibuprofen 200 mg) was used in the fish oil group (mean: 4.7 tablets with fish oil *v* 10.1 tablets with placebo; P = 0.015). The additional RCT (78 women with primary dysmenorrhoea) compared four interventions: fish oil (0.5–1.0 g 5 times daily); fish oil plus vitamin B_{12}; seal oil (higher in saturated fat than fish oil); and placebo for a minimum of 3 months. [43] It found no significant difference between fish oil and placebo in pain as measured on a 10 cm visual analogue scale (mean reduction in scores: 0.15 cm with fish oil *v* 0.19 cm with placebo; P = 0.62)

Harms: **Fish oil versus placebo:**
The RCT identified by the review found that two women taking fish oils reported nausea and one woman reported acne. [24] No adverse effects were reported in women receiving placebo. The additional RCT did not report adverse effects in each group separately. [43] Adverse effects reported in 8 women in the study included stomach upset, slight nausea and bad taste.

Comment: Both RCTs included women with dysmenorrhoea and no additional health problems. [24] [43] This could include women with either primary or secondary dysmenorrhoea. The results from the RCT identified by the review refer to the average of the two groups after the allocated treatments were crossed over, and should be interpreted with caution, as treatment effects may persist after crossover. [24]

OPTION HERBAL REMEDIES OTHER THAN TOKI-SHAKUYAKU-SAN

Pain

Rose tea compared with waiting list control We don't know whether rose tea is more effective than a waiting list control at reducing pain at 6 months in women with dysmenorrhoea (very low-quality evidence).

Note

We found no clinically important results about any herbal remedies other than rose tea or toki-shakuyaku-san in women with dysmenorrhoea.

For GRADE evaluation of interventions for dysmenorrhoea, **see table, p 23 .**

Benefits:

Rose tea:
One RCT (130 women with primary dysmenorrhoea, aged 15–18 years) compared drinking rose tea (2 teacups a day made from 6 dry rosebuds steeped in 300 mL of hot water, taken for 12 days from 1 week before the start of menses to the fifth menstrual day) versus a waiting list control. [44] The RCT found no significant differences in changes from baseline in any outcome measures between rose tea and control at up to 6 months (mean difference in change in Short Form McGill Pain questionnaire at 6 months: –1.76; Visual Analogue Scale for Anxiety: –0.04; Perceived Stress Scale: –1.58; Menstrual Distress Questionnaire –Short Form: –1.44; all differences reported as not significant, P values not reported). However, when the RCT adjusted for differences in age and the Perceived Stress Scale scores at baseline, it found that rose tea improved scores from baseline significantly more than control at up to 6 months ($P < 0.001$ for all scales).

Other herbal remedies:
We found no RCTs of other herbal remedies.

Harms:

Rose tea:
Two women reported mild diarrhoea after drinking the first course of rose tea. [44] One woman withdrew as a result, the other continued and experienced no further diarrhoea.

Other herbal remedies:
We found no RCTs.

Comment: None.

OPTION MAGNESIUM

Pain
Compared with placebo We don't know whether magnesium is more effective than placebo at reducing pain at 4–6 months in women with primary dysmenorrhoea (very low-quality evidence).

Benefits:

Magnesium versus placebo:
We found one systematic review (search date 2000, 3 RCTs). [24] The first RCT (50 women) identified by the review compared magnesium aspartate (20 mmol 3 times daily) versus placebo. It found that magnesium aspartate significantly increased the proportion of women without pain after 6 months compared with placebo (21/25 [84%] with magnesium aspartate *v* 7/25 [28%] with placebo; RR 3.0, 95% CI 1.6 to 5.8; NNT 2, 95% CI 2 to 3). The second RCT (27 women) identified by the review found no significant difference between magnesium (5 mmol 3 times daily) and placebo in reducing pain, as measured by visual analogue scale pain scores, or in the number of ibuprofen tablets taken after 4 months ($P = 0.07$; no further data reported). The third RCT (21 women) identified by the review found that magnesium (500 mg/day during menses) significantly reduced pain measured on a 3 point scale after 5 months compared with placebo (absolute numbers not reported; $P < 0.01$). [24]

Harms:

Magnesium versus placebo:
The first RCT identified by the review found that magnesium aspartate significantly increased the proportion of women who experienced intestinal discomfort and other minor adverse effects compared with placebo (5/25 [20%] with magnesium aspartate *v* 0/25 [0%] with placebo; NNH 5, 95% CI 2 to 38), although relief of these symptoms occurred when the dose was reduced from three to two tablets daily. [24]

Comment: None.

OPTION MAGNETS New

Pain
Compared with 'placebo' magnet Magnets may reduce pain for up to 3 hours after application compared with application of non-magnets in women with primary dysmenorrhoea (low-quality evidence).

For GRADE evaluation of interventions for dysmenorrhoea, **see table, p 23 .**

Benefits:

One RCT (23 women with primary dysmenorrhoea) compared an applied magnet (800–1299 gauss for 3 hours on the first day of pain) versus a control group that applied a non-magnet to the suprapubic area, lumbar area, and inner ankles (English abstract only). [45] The RCT found magnet treatment significantly improved pain and symptom scores compared with control immediately after treatment (Graphic Rating Scale, $P = 0.0001$; Adjective Labour Pain Rating Scale Rank, $P = 0.01$;

and Adjective Labour Pain Rating Scale Score; P = 0.009). Magnet treatment also improved pain and symptom scores compared with control 3 hours after treatment (Graphic Rating Scale, P = 0.007; Adjective Labor Pain Rating Scale, P = 0.032; and Adjective Labour Pain Rating Scale Score, P = 0.037).

Harms: The English language abstract of the RCT did not present any information on adverse effects. [45]

Comment: Limited information was available from the English language abstract of this RCT. [45] The RCT is currently being translated from Korean to English.

OPTION SURGICAL INTERRUPTION OF PELVIC NERVE PATHWAYS

Pain

Laparoscopic uterine nerve ablation compared with diagnostic laparoscopy Laparoscopic uterine nerve ablation may reduce pain at 12 months, but not at 6 months, compared with diagnostic laparoscopy (low-quality evidence).

Laparoscopic uterine nerve ablation compared with presacral neurectomy Laparoscopic uterine nerve ablation may be less effective than laparoscopic presacral neurectomy at reducing pain at 12 months, but not at 3 months (low-quality evidence).

Adverse effects

Laparoscopic presacral neurectomy has been asociated with constipation.

Benefits: We found one systematic review (search date 2004, 9 RCTs) of surgical pelvic nerve interruption for primary and secondary dysmenorrhoea. [46] Three of the nine RCTs (136 women) identified by the review included women with primary dysmenorrhoea. The remainder included women with dysmenorrhoea associated with endometriosis or uterine myomas, which is not the focus of this review.

Laparoscopic uterine nerve ablation versus diagnostic laparoscopy:
Two RCTs identified by the review compared laparoscopic uterine nerve ablation (LUNA) versus diagnostic laparoscopy for women with primary dysmenorrhoea and found that LUNA was more effective than control at 12 months (2 RCTs, 68 women; RR 3.94, 95% CI 1.45 to 10.66) but not at 6 months postoperative (2 RCTs, 68 women; RR 1.33, 95% CI 0.60 to 2.94). There was no significant difference between groups in satisfaction rates at 12 months (15/18 [83%] with LUNA *v* 22/32 [69%] with control; P > 0.05). [46]

Laparoscopic uterine nerve ablation versus laparoscopic presacral neurectomy:
The third RCT (68 women) identified by the review found no significant difference between LUNA and laparoscopic presacral neurectomy (LPSN) in pain relief at 3 months' follow up (RR 0.94, 95% CI 0.77 to 1.15). However, at 12 months' follow up, the LPSN group had significantly better pain relief scores (RR 0.38, 95% CI 0.23 to 0.64). [46]

Harms: **Laparoscopic uterine nerve ablation versus diagnostic laparoscopy:**
The review gave no information on adverse effects. [46]

Laparoscopic uterine nerve ablation versus laparoscopy presacral neurectomy:
One RCT identified by the review found that LPSN increased constipation compared with LUNA (31/33 [94%] with LPSN *v* 0/35 [0%] with LUNA; RR 0.01, 95% CI 0 to 0.24). [46]

Comment: One large RCT of LUNA is underway, and data will be included in an update of the systematic review (Proctor M, personal communication, 2005). [47] We found a second relevant systematic review but have not included this because it includes lower levels of evidence, such as case studies. [48]

OPTION VITAMIN B12

Note

We found no clinically important results about the effects of vitamin B_{12} compared with no active treatment, in women with primary dysmenorrhoea.

For GRADE evaluation of interventions for dysmenorrhoea, see table, p 23 .

Benefits: **Vitamin B_{12} versus placebo:**
We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: None.

OPTION SPINAL MANIPULATION

Pain

High-velocity low-amplitude spinal manipulation compared with placebo manipulation High-velocity low-amplitude spinal manipulation may be no more effective at reducing pain compared with placebo manipulation in women with primary dysmenorrhoea at 1 month (very low-quality evidence).

For GRADE evaluation of interventions for dysmenorrhoea, see table, p 23 .

Benefits: We found one systematic review (search date 2006, 3 RCTs meeting *BMJ Clinical Evidence* inclusion criteria), which compared spinal manipulation versus placebo or no treatment. [49] The review did not perform a meta-analysis because of heterogeneity among the trials in methods of spinal manipulation used, parts of the spine manipulated, and duration of treatment. The largest RCT (138 women) identified by the review found no significant difference in pain (as measured by mean change in visual analogue scale pain score) between high velocity, low amplitude (HVLA) manipulation compared with placebo manipulation after one menstrual cycle (WMD +2.08, 95% CI –3.20 to +7.36). The second RCT identified by the review (44 women) found that HVLA manipulation significantly reduced pain intensity, as measured by a 10 cm visual analogue scale pain score after one treatment and one menstrual cycle, compared with placebo manipulation (WMD –1.41, 95% CI –2.55 to –0.27). The third RCT (26 women) identified by the review compared 3 months of Toftness manipulation versus placebo manipulation. It found that manipulation significantly reduced pain intensity after 6 months compared with placebo, but not at 3 months (WMD at 6 months –1.40, 95% CI –2.21 to –0.59; WMD at 3 months 2.20, 95% CI 1.38 to 3.02). [49]

Harms: One RCT (138 women) identified by the review found no significant difference between HVLA manipulation and placebo manipulation in the proportion of women experiencing soreness in the lower back region within 48 hours of the intervention (3/69 [4%] with HVLA manipulation *v* 2/69 [3%] with placebo manipulation; RR 1.50, 95% CI 0.26 to 8.70). [49] Soreness resolved within 24 hours. No other adverse effects were reported. The other RCTs identified by the review gave no information on adverse effects.

Comment: Two of the three studies included in the review had small sample sizes and methodological weaknesses, such as inadequate allocation concealment, and lack of blinding of outcome assessors. The study receiving the highest methodological score was also the largest study, and was therefore considered to be the most reliable.

GLOSSARY

Behavioural interventions Treatments attempting modification of thought and beliefs (cognition) about symptoms and pain, or treatments that attempt modification of behavioural or physiological responses to symptoms, pain, or both; for example, relaxation and exercise.
Co-proxamol Non-proprietary label for a dextropropoxyphene hydrochloride and paracetamol combination. The most common formulation is dextropropoxyphene hydrochloride 32.5 mg and paracetamol 325 mg.
Congestive dysmenorrhoea A dull aching pain in the lower abdomen as well as other areas of the body that may begin several days before menstruation and can include other premenstrual symptoms such as irritability. [50]
Double dummy Design pertaining to an RCT in which multiple treatments are compared (usually against a placebo) and the treatments have dissimilar presentations. Each participant will receive either active treatment or placebo for each treatment. Because multiple treatments are being compared (at least 2), it allows identification of treatment effects against placebo, as well as the additive effects of treatments.
Efficacy RCT A trial designed to study if an intervention works in ideal conditions (e.g. when people receive treatments exactly as prescribed). By contrast, effectiveness trials evaluate the effects of treatments in “real life” conditions. Analysis in efficacy trials usually involves only the participants who were fully compliant with the therapeutic regimen. The applicability of the results from efficacy trials may be limited because conditions are artificial and hence response may be different in real life situations.
High velocity, low amplitude (HVLA) manipulation A technique of spinal manipulation that uses high velocity, low amplitude thrusts to manipulate vertebral joints. The technique is designed to restore motion to a restricted joint and improve function. The physician positions the person at the barrier of restricted motion and then gives a rapid, accurate thrust in the direction of the restricted barrier to resolve the restriction and improve motion.
Laparoscopic presacral neurectomy (LPSN) Involves the total removal of the presacral nerves lying within the boundaries of the interiliac triangle. This procedure interrupts most of the cervical sensory nerve fibres and is used to diminish uterine pain.
Laparoscopic uterine nerve ablation (LUNA) Involves laparoscopic surgery to transect (usually involves cutting and then electrocauterisation) the uterosacral ligaments at their insertion into the cervix. This procedure interrupts most of the cervical sensory nerve fibres and is used to diminish uterine pain.

Placebo acupuncture Also known as sham acupuncture, this is a commonly used control intervention involving the use of acupuncture needles to stimulate non-acupuncture points in areas outside of Chinese meridians. These points can be identified by a point detector as areas of the skin that do not have skin electrical activity similar to acupuncture points. There is some disagreement over correct needle placement, as placement of a needle in any position may elicit some biological response that can complicate the interpretation of results.
Placebo manipulation Also known as sham manipulation, this is a control intervention. The main principle is to use a non-therapeutic level of torque. There are two common techniques for placebo manipulation. In one, thrust is given but the posture of the participant is such that the mechanical torque of the manipulation is substantially reduced. In the other, an activator adjusting tool is used; this can make spinal adjustments using spring recoil, whereby the spring is set so that no force is exerted on the spine.
SPID-8 An outcome measure commonly used in pharmaceutical trials of treatments for pain. The difference in pain intensity from baseline up to 8 hours after dosing is measured. The SPID-8 is the sum of the pain intensity differences of all participants up to 8 hours after dosing. Pain intensity can be measured on any categorical scale, but typically a low score will mean less pain and a high score more pain.
Spasmodic dysmenorrhoea Spasms of acute pain that typically begin on the first day of menstruation. [30]
TOTPAR (TOPAR) score An outcome measure commonly used in pharmaceutical trials of treatment for pain. The pain relief scores for all participants at various time points after dosing are totalled and a mean calculated. Pain relief can be measured on any categorical scale, but typically a low score will mean less pain relief and a high score more pain relief.
TOTPAR-8 (TOPAR-8) score The same as TOTPAR (see above), but measured up to 8 hours after dosing.
Toftness manipulation A low force technique of chiropractic adjustment that uses a sensometer to detect sites of abnormal electromagnetic radiation, and to determine which sites to adjust. Adjustment is then delivered using a metered, hand held pressure applicator.
Transcutaneous electrical nerve stimulation (TENS) Electrodes are placed on the skin and different electrical pulse rates and intensities are used to stimulate the area. Low frequency TENS (also referred to as acupuncture-like TENS) usually consists of pulses delivered at 1–4 Hz at high intensity, so they evoke visible muscle fibre contractions. High frequency TENS (conventional TENS) usually consists of pulses delivered at 50–120 Hz at a low intensity, so there are no muscle contractions.
Visual analogue scale A commonly used scale in pain assessment. It is a 10 cm horizontal or vertical line with word anchors at each end, such as “no pain” and “pain as bad as it could be”. The person is asked to make a mark on the line to represent pain intensity. This mark is converted to distance in either centimetres or millimetres from the “no pain” anchor to give a pain score that can range from 0 to 10 cm or 0 to 100 mm.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

New option added Acupressure.
Magnets New option added; categorised as Unknown effectiveness as only one small RCT showing they may be effective in women with primary dysmenorrhoea.
Behavioural interventions One systematic review added; [35] categorisation unchanged (Unknown effectiveness) but benefits data enhanced.
Combined oral contraception One RCT added; [40] categorisation unchanged (Unknown effectiveness) but benefits and harms data enhanced.
Herbal remedies other than toki-shakuyaku-san One RCT added; [44] categorisation unchanged (Unknown effectiveness) but benefits and harms data enhanced.

REFERENCES

1. Fraser I. Prostaglandins, prostaglandin inhibitors and their roles in gynaecological disorders. *Baillière's Clinical Obstet Gynaecol* 1992;6:829–857.
2. Zondervan KT, Yudkin PL, Vessey MP, et al. The prevalence of chronic pelvic pain in the United Kingdom: a systematic review. *Br J Obstet Gynaecol* 1998;105:93–99. Search date 1996; primary sources Medline, Embase, and Psychlit.[PubMed]
3. Harlow SD, Campbell OM. Epidemiology of menstrual disorders in developing countries: a systematic review. *BJOG* 2004;111:6–16. Search date 2002.[PubMed]
4. Harlow SD, Park M. A longitudinal study of risk factors for the occurrence, duration and severity of menstrual cramps in a cohort of college women. *Br J Obstet Gynaecol* 1996;103:1134–1142. [Erratum in: *Br J Obstet Gynaecol* 1997;104:386] [PubMed]
5. Campbell MA, McGrath PJ. Use of medication by adolescents for the management of menstrual discomfort. *Arch Pediatr Adolesc Med* 1997;151:905–913.[PubMed]
6. Robinson JC, Plichta S, Weisman CS, et al. Dysmenorrhoea and the use of oral contraceptives in adolescent women attending a family planning clinic. *Am J Obstet Gynecol* 1992;166:578–583.[PubMed]
7. Andersch B, Milsom I. An epidemiologic study of young women with dysmenorrhea. *Am J Obstet Gynecol* 1982;144:655–660.[PubMed]
8. Klein JR, Litt IF. Epidemiology of adolescent dysmenorrhea. *Pediatrics* 1981;68:661–664.[PubMed]
9. Patel V, Tanksale V, Sahasrabhojanee M, et al. The burden and determinants of dysmenorrhoea: a population-based survey of 2262 women in Goa, India. *BJOG* 2006;113:453–463.[PubMed]
10. Burnett MA, Antao V, Black A, et al. Prevalence of primary dysmenorrhea in Canada. *J Obstet Gynaecol Can* 2005;27:765–770.[PubMed]
11. Sundell G, Milsom I, Andersch B. Factors influencing the prevalence and severity of dysmenorrhoea in young women. *Br J Obstet Gynaecol* 1990;97:588–594.[PubMed]
12. Chen C, Cho SI, Damokosh AI, et al. Prospective study of exposure to environmental tobacco smoke and dysmenorrhea. *Environ Health Perspect* 2000;108:1019–1022.[PubMed]
13. Marjoribanks J, Proctor ML, Farquhar C. Nonsteroidal anti-inflammatory drugs for primary dysmenorrhoea. In: The Cochrane Library, Issue 2, 2006. Chichester: John Wiley & Sons. Search date 2003; primary sources Cochrane Menstrual Disorders and Subfertility Group Trials Register, Cochrane Controlled Trials Register, Medline, Embase, National Research Register, and hand searches of citation lists and conference proceedings.[PubMed]
14. Mehlisch DR, Ardia A, Pallotta T. Analgesia with ibuprofen arginate versus conventional ibuprofen for patients with dysmenorrhea: a crossover trial. *Curr Ther Res* 2003:64;327–337.
15. Malmstrom K, Kotey P, Cichanowitz N, et al. Analgesic efficacy of etoricoxib in primary dysmenorrhea: results of a randomized, controlled trial. *Gynecol Obstet Invest* 2003;56:65–69.[PubMed]

16. de Mello NR, Baracat EC, Tomaz G, et al. Double-blind study to evaluate efficacy and safety of meloxicam 7.5 mg and 15 mg versus mefenamic acid 1500 mg in the treatment of primary dysmenorrhea. *Acta Obstet Gynecol Scand* 2004;83:667–673.[PubMed]
17. Zhang WY, Li Wan Po A. Efficacy of minor analgesics in primary dysmenorrhoea: a systematic review. *Br J Obstet Gynaecol* 1998;105:780–789. Search date 1997; primary sources Medline, Embase, and Science Citation Index.[PubMed]
18. Anderson ABM, Haynes PJ, Fraser IS, et al. Trial of prostaglandin-synthetase inhibitors in primary dysmenorrhoea. *Lancet* 1978;1:345–348.
19. Langrick AF, Gunn ADG. A comparison of naproxen sodium and a dextropropoxyphene/paracetamol combination in the treatment of primary dysmenorrhoea in university health centres. *Br J Clin Pract* 1982;36:181–184.[PubMed]
20. Williams AA, Backhouse CI. A general practice study of naproxen sodium and a dextropropoxyphene paracetamol combination in primary dysmenorrhoea. *Br J Clin Pract* 1982;36:383–385.[PubMed]
21. Ylikorkala O, Puolakka J, Kauppila A. Comparison between naproxen tablets and suppositories in primary dysmenorrhea. *Prostaglandins* 1980;20:463–468.[PubMed]
22. Taylor D, Miaskowski C, Kohn J. A randomized clinical trial of the effectiveness of an acupressure device (relief brief) for managing symptoms of dysmenorrhea. *J Altern Complement Med* 2002;8:357–370.[PubMed]
23. Pouresmail Z, Ibrahimzadeh R. Effects of acupressure and ibuprofen on the severity of primary dysmenorrhea. *J Tradit Chin Med* 2002;22:205–210.[PubMed]
24. Proctor ML, Murphy PA. Herbal and dietary therapies for primary and secondary dysmenorrhoea. In: The Cochrane Library, Issue 2, 2006. Chichester: John Wiley & Sons. Search date 2000; primary sources Medline, Embase, Cinahl, Psychlit, Bioabstracts, Cochrane Controlled Trials Register, and hand searches of citation lists.[PubMed]
25. Zhu X, Smith C, Bensoussan A. Chinese herbal medicine for primary dysmenorrhoea (Cochrane protocol). In: The Cochrane Library, Issue 2, 2006. Chichester: John Wiley & Sons.
26. Akin MD, Weingand KW, Hengehold DA, et al. Continuous low-level topical heat in the treatment of dysmenorrhea. *Obstet Gynecol* 2001;97:343–349.[PubMed]
27. Akin M, Price W, Rodriguez G Jr, et al. Continuous, low-level, topical heat wrap therapy as compared to acetaminophen for primary dysmenorrhea. *J Reprod Med* 2004;49:739–745.[PubMed]
28. Proctor ML, Smith CA, Farquhar CM, et al. Transcutaneous electrical nerve stimulation and acupuncture for primary dysmenorrhoea. In: The Cochrane Library, Issue 2, 2006. Chichester: John Wiley & Sons. Search date 2001; primary sources Cochrane Central Register of Controlled Trials, Medline, Embase, Cinahl, Bio extracts, Psychlit, SportDiscus, Cochrane Complementary Medicine Field's Register of Controlled Trials (CISCOM), and hand searches of citation lists.[PubMed]
29. Dawood MY, Ramos J. Transcutaneous electrical nerve stimulation (TENS) for the treatment of primary dysmenorrhea: a randomized crossover comparison with placebo TENS and ibuprofen. *Obstet Gynecol* 1990;75:656–660.[PubMed]
30. Hedner N, Milsom I, Eliasson T, et al. TENS is effective in painful menstruation. *Lakartidningen* 1996;93:1219–1222. [In Swedish][PubMed]
31. Fugh-Berman A, Kronenberg F. Complementary and alternative medicine (CAM) in reproductive-age women: a review of randomized controlled trials. *Reprod Toxicol* 2003:17;137–152. Search date 2002; primary sources Medline, Alternative and Complementary Database, and hand searches of citation lists.[PubMed]
32. Ziaei S, Zakeri M, Kazemnejad A. A randomised controlled trial of vitamin E in the treatment of primary dysmenorrhoea. *BJOG* 2005;112:466–469.[PubMed]
33. Ziaei S, Faghihzadeh S, Sohrabvand F, et al. A randomised placebo-controlled trial to determine the effect of vitamin E in treatment of primary dysmenorrhoea. *BJOG* 2001;108:1181–1183.[PubMed]
34. Helms JM. Acupuncture for the management of primary dysmenorrhea. *Obstet Gynecol* 1987;69:51–56.[PubMed]
35. Fugh-Berman A, Kronenberg F. Complementary and alternative medicine (CAM) in reproductive-age women: a review of randomized controlled trials. *Reprod Toxicol* 2003;17:137–152. Search date 2002; primary sources Medline, Alternative and Complementary Database, and papers known to the authors.[PubMed]
36. Chesney MA, Tasto DL. The effectiveness of behavior modification with spasmodic and congestive dysmenorrhea. *Behav Res Ther* 1975;13:245–253. [PubMed]
37. Israel RG, Sutton M, O'Brien KF. Effects of aerobic training on primary dysmenorrhea symptomatology in college females. *J Am Coll Health* 1985;33:241–244.[PubMed]
38. Proctor ML, Roberts H, Farquhar C. Combined oral contraceptive pill as treatment for primary dysmenorrhoea. In: The Cochrane Library, Issue 2, 2006. Chichester: John Wiley & Sons. Search date 1999; primary sources Medline, Embase, Cinahl, Cochrane Register of Controlled Trials, and hand searches of citation lists.[PubMed]
39. Hendrix SL, Alexander NJ. Primary dysmenorrhea treatment with a desogestrel-containing low-dose oral contraceptive. *Contraception* 2002:66;393–399.[PubMed]
40. Davis AR, Westhoff C, O'Connell K, et al. Oral contraceptives for dysmenorrhea in adolescent girls: a randomized trial. *Obstet Gynecol* 2005;106:97–104.[PubMed]
41. Nakano R, Takemura H. Treatment of function dysmenorrhoea: a double-blind study. *Acta Obstet Gynaecol Jpn* 1971;18:41–44.[PubMed]
42. Matthews AE, Clarke JE. Double-blind trial of a sequential oral contraceptive (Sequens) in the treatment of dysmenorrhoea. *J Obstet Gynaecol Br Commonw* 1968;75:1117–1122.[PubMed]
43. Deutch B, Jorgensen EB, Hansen JC. Menstrual discomfort in Danish women reduced by dietary supplements of omega-3 PUFA and B12 (fish oil or seal oil capsules). *Nutr Res* 2000;20:621–631.
44. Tseng YF, Chen CH, Yang YH. Rose tea for relief of primary dysmenorrhea in adolescents: a randomized controlled trial in Taiwan. *J Midwifery Womens Health* 2005;50:e51–e57.[PubMed]
45. Kim KS, Lee YJ. The effect of magnetic application for primary dysmenorrhea. *Kanhohak Tamgu* 1994;3:148–173. [In Korean][PubMed]
46. Proctor ML, Latthe P, Farquhar CM, et al. Surgical interruption of pelvic nerve pathways for primary and secondary dysmenorrhoea. In: The Cochrane Library, Issue 2, 2006. Chichester: John Wiley & Sons. Search date 2004; primary sources Medline, Embase, Cinahl, Cochrane Central Register of Controlled Trials, and hand searches of citation lists and conference proceedings.[PubMed]
47. Birmingham Women's Health Care NHS Trust. An RCT to assess the efficacy of laparoscopic uterosacral nerve ablation (LUNA) in the treatment of chronic pelvic pain. *The National Research Register* 2002; 4:N0047063419. http://www.nrr.nhs.uk/ (last accessed 12 January 2007).
48. Khan KS, Khan SF, Nwosu CR, et al. Laparoscopic uterosacral nerve ablation in chronic pelvic pain: an overview. *Gynaecol Endosc* 1999;8:257–265. Search date 1997; primary sources Medline, Embase, and Science Citation Index.
49. Proctor ML, Hing W, Johnson TC, et al. Spinal manipulation for primary and secondary dysmenorrhoea. In: The Cochrane Library, Issue 2, 2006. Chichester: John Wiley & Sons. Search date 2006; primary sources Medline, Embase, Cinahl, Psychlit, Amed, Bioabstracts, SportDiscus, Cochrane Central Register of Controlled Trials, and hand searches of citation lists.[PubMed]
50. Rosenwaks Z, Jones GS, Henzl MR, et al. Naproxen sodium, aspirin, and placebo in primary dysmenorrhoea. Reduction of pain and blood levels of prostaglandin-F2-alpha metabolite. *Am J Obstet Gynecol* 1981:140;592–598.[PubMed]

Michelle L Proctor
Cochrane Review Group Co-ordinator
Cochrane Menstrual Disorders and Subfertility Group
Department of Obstetrics and Gynaecology, University of Auckland
Auckland
New Zealand

Cynthia M Farquhar
School of Medicine
University of Auckland
Auckland
New Zealand

Competing interests: MP is the co-author of six systematic reviews ([13] , [24] , [28] , [38] , [46] and [49]) that are referenced in this review. CF is the co-author of four systematic reviews ([13] , [28] , [38] and [48]) that are referenced in this review.

Disclaimer

The information contained in this publication is intended for medical professionals. Categories presented in Clinical Evidence indicate a judgement about the strength of the evidence available to our contributors prior to publication and the relevant importance of benefit and harms. We rely on our contributors to confirm the accuracy of the information presented and to adhere to describe accepted practices. Readers should be aware that professionals in the field may have different opinions. Because of this and regular advances in medical research we strongly recommend that readers' independently verify specified treatments and drugs including manufacturers' guidance. Also, the categories do not indicate whether a particular treatment is generally appropriate or whether it is suitable for a particular individual. Ultimately it is the readers' responsibility to make their own professional judgements, so to appropriately advise and treat their patients. To the fullest extent permitted by law, BMJ Publishing Group Limited and its editors are not responsible for any losses, injury or damage caused to any person or property (including under contract, by negligence, products liability or otherwise) whether they be direct or indirect, special, incidental or consequential, resulting from the application of the information in this publication.

TABLE 1 **Prevalence of dysmenorrhoea: results of community and hospital surveys (see text).** [4] [5] [6] [7] [8] [9] [10]

Study population	Population size	Location	Year	Prevalence
College students aged 17–19 years [4]	165	USA	1996	72% (13% severe)
High school students aged 14–21 years [5]	291	Canada	1997	93% (5% severe)
Adolescents attending an inner city family planning clinic [6]	308	USA	1992	80% (18% severe)
Women from an urban population aged 19 years [7]	596	Sweden	1982	73% (15% severe)
Adolescents aged 12–17 years [8]	2699	USA	1981	60% (14% severe)
Women aged 18–45 years [9]	2262	India	2006	55% (18% severe)
Women aged less-than or equal to 18 years [10]	1546	Canada	2005	60% primary dysmenorrhoea (36% moderate or severe) 5% secondary dysmenorrhoea

TABLE 2 **Effects of aspirin, paracetamol, and compound analgesics for dysmenorrhoea: results of two systematic reviews (see text, p 7).** [13] [17]

Comparison	Usual dosage	Number of RCTs	Number of women	Pain relief	Adverse effects	Conclusion
Aspirin *v* placebo	650 mg 4 times daily	8	486	RR 1.60, 95% CI 1.12 to 2.29, NNT 10, 95% CI 5 to 50	No significant difference (7–17% with aspirin *v* 3–17% with placebo; RR 1.3, 95% CI 0.79 to 2.17). [17] No significant difference (50% with aspirin *v* 33% with placebo; OR 1.93, 95% CI 0.49 to 7.62) [13]	Aspirin more effective than placebo
Aspirin *v* paracetamol	650 mg *v* 500 mg 4 times daily	1	35	Median pain relief: 1.6, 95% CI 0.4 to 3.3 with paracetamol *v* 1.2, 95% CI 0 to 2.7 with aspirin	NA	No significant difference
Aspirin *v* naproxen	650 mg *v* 275 mg 4 times daily	1	32	RR 2.29, 95% CI 1.09 to 4.79	NA	Naproxen more effective than aspirin
Paracetamol *v* naproxen	1000 mg *v* 220 mg up to 3 times daily	1	117	RR 1.68, 95% CI 0.86 to 3.26	No significant difference. RR 1.00, 95% CI 0.06 to 15.43 for gastrointestinal	No significant difference
Aspirin *v* ibuprofen	650 mg *v* 400 mg 4 times daily	1	56	RR 1.90, 95% CI 1.13 to 2.78	NA	Ibuprofen more effective than aspirin
Paracetamol *v* placebo	500 mg 4 times daily	1	35	RR 1.00, 95% CI 0.28 to 3.63	No significant difference; RR 1.00, 95% CI 0.36 to 2.75	No significant difference
Paracetamol *v* ibuprofen	1000 mg *v* 400 mg 3 times daily	1	67	RR 0.86, 95% CI 0.68 to 1.10	No significant difference: OR 1.00, 95% CI 0.06 to 16.58 for gastrointestinal; OR 1.54, 95% CI 0.24 to 9.78 for nervous system	No significant difference
Co-proxamol *v* placebo	650 mg/65 mg 4 times daily	1	72	RR 3.72, 95% CI 2.13 to 6.52	NA	Co-proxamol more effective than placebo
Co-proxamol *v* naproxen	650 mg/65 mg *v* 275 mg 3 times daily	2	98	P > 0.05 (no other data could be obtained from the report)	More frequent on co-proxamol: 23–58% with co-proxamol *v* 15–25% with naproxen; RR 1.94, 95% CI 1.11 to 3.41	No significant difference
Co-proxamol *v* mefenamic acid	650 mg/65 mg *v* 500 mg 3 times daily	1	30	P < 0.01 (no other evidence can be obtained from the trial)	NA	Mefenamic acid more effective than co-proxamol

NA, not available.

TABLE GRADE evaluation of interventions for dysmenorrhoea

Important outcomes	Pain, severity of dysmenorrhoea, quality of life, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for dysmenorrhoea?									
16 (776) [13] [14] [15]	Pain	NSAIDs *v* placebo	4	–2	–1	–1	0	Very low	Quality point deducted for unclear randomisation methodology and incomplete reporting of results. Consistency point deducted for conflicting results with niflumic acid. Directness point deducted for inadequate methods for assessing outcomes
At least 4 RCTs (at least 229) [13]	Daily activities and work	NSAIDs *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for unclear randomisation methodology. Directness point deducted for inadequate methods for assessing outcomes
6 (972) [13] [14] [15] [16]	Pain	Different NSAIDs compared with each other	4	–2	0	–1	0	Very low	Quality point deducted for unclear randomisation methodology and incomplete reporting of results. Directness point deducted for inadequate methods for assessing outcomes
2 (184) [17] [13]	Pain	NSAIDs *v* paracetamol	4	–2	0	–1	0	Very low	Quality point deducted for sparse data and unclear randomisation methodology. Directness point deducted for inadequate methods for assessing outcomes
2 (88) [17] [13]	Pain	NSAIDs *v* aspirin	4	–2	0	–1	0	Very low	Quality point deducted for sparse data and unclear randomisation methodology. Directness point deducted for inadequate methods for assessing outcomes
3 (154) [18] [19] [20]	Pain	NSAIDs *v* co-proxamol	4	–3	–1	–1	0	Very low	Quality point s deducted for sparse data, unclear randomisation methodology, and incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for inadequate methods for assessing outcomes
2 (44) [29] [30]	Pain	NSAIDs *v* TENS	4	–3	–1	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and lack of blinding. Consistency point deducted for conflicting results
1 (50) [24]	Pain	Ibuprofen plus vitamin E *v* ibuprofen alone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (216) [23]	Pain	Ibuprofen *v* acupressure *v* sham acupressure	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (84) [26]	Pain	Heated patch plus ibuprofen *v* heated patch plus placebo *v* unheated patch plus ibuprofen *v* unheated patch plus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of volunteer women as well as those presenting for medical care
2 (277) [22] [23]	Pain	Acupressure *v* usual care or sham acupressure	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
At least 8 (at least 486) [13] [17]	Pain	Aspirin *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for poor follow-up. Consistency point deducted for conflicting results
1 (35) [17]	Pain	Paracetamol *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and poor follow-up
1 (72) [17]	Pain	Co-proxamol *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and poor follow-up

Important outcomes	Pain, severity of dysmenorrhoea, quality of life, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (35) [17]	Pain	Aspirin *v* paracetamol	4	–2	0	0	0	Low	Quality points deducted for sparse data and poor follow-up
1 (344) [27]	Pain	Paracetamol *v* topical heat	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (556) [24]	Pain	Thiamine *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for restricted population (indian adolescent women).
1 (50) [24]	Pain	Toki-shakuyaku-san *v* placebo	4	–3	0	0	0	Low	Quality points deducted for sparse data, unclear allocation methodology, and incomplete reporting of results
1 (84) [27]	Pain	Topical heat plus placebo *v* unheated patch plus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of volunteer women
3 (71) [28]	Pain	High-frequency TENS *v* placebo stimulation	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (53) [28]	Pain	Low-frequency TENS *v* placebo TENS	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
2 (41) [28]	Pain	Low-frequency TENS *v* placebo tablets	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
3 (at least 39) [28]	Pain	High-frequency TENS *v* Low frequency TENS	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
3 (478) [33] [31] [32]	Pain	Vitamin E *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (43) [28]	Pain	Acupuncture *v* placebo acupuncture *v* medical visits *v* no care	4	–2	0	0	0	Low	Quality points deducted for sparse data and use of unvalidated scoring system
1 (69) [36]	Pain	Relaxation treatment *v* waiting list control	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
1 (36) [37]	Pain	Exercise *v* sedentary lifestyle	4	–3	0	0	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results
7 (532) [38] [39] [40]	Pain	Combined oral contraceptives *v* placebo	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for use of obsolete treatments
2 (less than 120) [24] [43]	Pain	Fish oil *v* placebo	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and flawed crossover methodology. Consistency point deducted for conflicting results
1 (130) [44]	Pain	Rose tea *v* waiting list control	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
3 (98) [24]	Pain	Magnesium *v* placebo	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
1 (23) [45]	Pain	Magnet *v* placebo magnet	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (68) [46]	Pain	Laparoscopic uterine nerve ablation *v* diagnostic laparoscopy	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results

Important outcomes	Pain, severity of dysmenorrhoea, quality of life, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (68) [46]	Pain	Laparoscopic uterine nerve ablation *v* laparoscopic presacral neurectomy	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
3 (208) [49]	Pain	High-velocity, low-amplitude manipulation *v* placebo manipulation	4	–2	–1	0	0	Very low	Quality points deducted for sparse data, poor allocation concealment, and poor blinding. Consistency point deducted for conflicting results

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio